Applications of Epidemiological Methods to the Study of Congenital Malformations in Man

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INTRODUCTION.

PLANNED observation of phenomena as they occur must be the main tool of investigation in man, experiments as in animals being impossible, but planned observation and analysis is surely the very essence of epidemiology. Yet it would seem to be characteristic of work on human anomalies that many people are working directly on these, or on relevant problems, in narrow fields and making disconnected contributions to knowledge.

My general thesis is that many good opportunities for epidemiological work are being wasted because the hypotheses arising from different sources are not being tested adequately by the epidemiological method.

In countries which have achieved a very low level of fœtal and early life loss, these anomalies now account for as much as a quarter of all reproductive wastage. Therefore the problems they raise are urgent, and the approach to prevention, however uncertain at the moment, must await a better understanding of the many ætiological factors and consequent identification of specific cause and effect syndromes.

In this connection, it would seem that any holistic hypotheses which seem so attractive to many writers should not be taken too seriously in our present state of lack of knowledge, but rather be thought of as a possibility when we know more. It seems to me that a preconceived holistic theory, involving a kind of unity of lesser viability ranging from abortions, through prematurity and unexplained fœtal deaths to gross malformations, while conceivably applicable at present to certain individual mothers with genital abnormalities, would interfere with the need for the careful clinical and pathological definitive work necessary to isolate specific syndromes of cause, developmental mistake and resultant anomaly.

A. SOURCES OF KNOWLEDGE WHICH GIVE INDICATIONS OF ÆTIOLOGY.

I should like to review the main sources of knowledge which should be determining the planning of observations of human malformations and their environmental and maternal associations, and to point to their applications in the study of malformations in man.

(1) Animal Experimental Work.

Perhaps the outstanding demonstration from animal work has been the large number of tetragenic agents which are completely, or relatively completely, non-specific to the type of defect which they produce. Physical influences, nutritional imbalances, endocrines, anoxia, a wide variety of chemical agents and exposure to ionizing radiations have been shown to be capable of producing malformations when the animal is exposed to them at an appropriate period of her pregnancy. There are two points which stand out, however. The *first* is that there is apparently much more time than agent specificity to the type of malformation produced. The *second* is that the proportion of a litter affected is not only dependent on dosage, but for a given dosage, varies greatly between different strains of animal. In turn this time specificity has been related to events in the embryo, and broadly this suggests that tissues rapidly differentiating at the time of exposure are most susceptible to damage from all the tetragenic agents.

Animal experiments have also shown that the defects produced usually occur spontaneously in the stock and further that there are a considerable number of syndromes which are in fact determined by the mendelian mechanism of a single gene, usually recessive. This last particularly applies to some central nervous system anomalies, and in them it is clear that there are groups of syndromes, distinguished with difficulty, if at all, clinically or even by morbid anatomy, which can be determined by independent (and non-linked) genes.

The embryo-pathology of many of these defects has been very carefully studied by Gruneberg (1947 and many subsequent papers) and others, and the starting point of an anomaly and the steps leading to the fully developed end picture traced in a manner quite impossible in man. Finally, in drosophila work, it has been demonstrated that chromosome damage, induced in the male by radiation, can be transmitted to subsequent generations in a pattern which can be reconciled with a translocation observed cytologically. Perhaps even more interesting is the highly suggestive evidence that chromosome translocations are similarly induced in, and transmitted by, mammal males and that in them, possibly irrespective of the precise situation and form of the translocations induced, one type of descendant shows anomalies of the neural tube (Snell and Picken (1935)).

In brief then, animal work suggests time rather than tetragenic agent specificity to the defect produced, that the action of the agent is not independent of hereditary variations in the strain of animal used, and that there are single gene expressions which can mimic induced defects. Finally, the possibility exists that in man also there may be at times a translocation effect.

(2) Embryology.

Human embryological literature still includes relatively little clear exposition of what is known of the timing of spurts of differentiation of complex and sensitive tissue in the embryo. Indeed too few embryologists seem particularly interested in such problems. The Carnegie Institute publications on "Developmental Horizons in Human Embryos" seem to stand alone as formal attempts to present what is

known in this field in a readily accessible form, but most text books signally fail to consider early developmental pathology or these timings and to relate them to the pathology observed in fœtuses reaching viable ages.

A few landmarks of timings are of course known and accepted, but still it is difficult to get firm agreed views of embryologists on the majority of timings in which obstetricians, pædiatricians and geneticists are interested.

(3) The Contributions of Fœtal and Neonatal Pathology.

It is surprising indeed that much that is fairly well defined in the morbid anatomy of the central nervous system anomalies, particularly the hydrocephaly, anencephaly, iniencephaly, spina bifida, meningocœle series, has been so little taken into account in epidemiological studies. It seems quite illogical to submit data on "hydrocephaly" as a homogeneous entity to elaborate numerical treatment when the morbid anatomy indicates that there are several syndromes and when even clinical observation can, with reasonable accuracy, separate out several distinct types. Thus the Arnold-Chiari malformation of cerebellum, with herniation of the cerebellum and abnormal tongues of vascular tissue into the foramen magnum, seems to be the most common cause of hydrocephalus present at birth in the United Kingdom and North America. It is very commonly associated with marked lumbo-sacral spina bifida which is almost invariably of the meningo-myelocœle type. Further, in cases of large spina bifida, especially meningo-myelocœles, autopsy usually reveals the cerebellar anomaly even if there is no obvious hydrocephalus at the time of death. Probably the condition is detectable in life in a high proportion of cases or even before birth, by X-ray demonstration of cranio-lacunæ which seldom or ever occur in other types of hydrocephalus. Only occasionally is the malformation occult, but it may give rise to trouble in the teens. An odd case has even been reported as a chance autopsy finding in later life.

Quite distinct are the varieties of hydrocephalus from blocking of the æqueduct of Sylvius or the foramina of Magendie which are much less commonly detectable at birth but which characteristically come to notice when the child fails to thrive and the head starts to enlarge a few days or even weeks after birth. Some of these cases are conditioned by simple stenosis of the æqueduct, some by forking and some by neuroglial growth, but so far there is little information on the differentiation of associated clinical signs and symptoms. Spina bifida is not so commonly associated with atresia syndromes and when it is, it appears usually to be associated with a simple meningeal protrusion or with spina bifida occulta.

Gruenwald (1941) suggests that there are different morbid anatomical types of anencephaly; one where the neural tube apparently never closed and there is little evidence that meninges ever covered the remnants of brain tissue; another where there are some meninges covering brain tissue which developed more or less normally up to a certain point, there being ventricles present, and then degenerated and been eroded. Finally, he suggests that there is a type of anencephaly where peri-arterial rosettes may be noted in the brain tissue. Clearly any such separations,

if they can be confirmed and defined, are of the utmost importance in epidemiological investigations.

(4) Observations in Man of Maternal Fœtal Associations.

From a variety of sources a number of fairly firm associations have been established in man and some of these are easy to reconcile with information from animal experimental work. The observations fall conveniently into a few headings :—(a) abnormality of implantation sites, (b) noxious influences in pregnancy, (c) specific disorders of pregnancy, (d) parental age, parity and familial incidence.

(a) *The relationship of anomaly of the fœtus with abnormality of the implantation site.*

A high proportion of abnormal embryos in ectopic gestations has long been accepted (Mall, 1908), but there is evidence that whenever the implantation site is abnormal an unduly high proportion of embryos fail to develop properly. Thus many malformed fœtuses are observed when the mother has uterine fibroids or has malformation of the uterus. An interesting recent observation (Holmes, 1956) is of a child having bicornate uterus born to a mother similarly affected. Finally, there is the less clear-cut association of malformation with placenta prævia. As far as I can discover, Penrose's (1939) suggestion of an ætiological difference between central and lateral placenta prævia has not yet been related to fœtal malformations.

(b) *The relationship of anomalies of the fœtus with noxious influences affecting the fœtus directly or through the mother.*

The remarkable demonstration in man of the association between rubella infection of the mother (and effectively of the fœtus) with defects, the specificity of which depends on the timing of the infection, has stimulated much interest. The relationship attributable to infections earlier in pregnancy than those causing the ear, eye and cardiac defects is, however, much less well established although not necessarily incorrect. There are also the known effects of toxoplasmosis infection of the fœtus and possibly of vaccinia. However, in spite of a good deal of broad reference to the "effects of virus infections in pregnancy," it should be remembered that, as yet, no other infections than the above have been definitely shown to be tetrangenic. There is also the relatively scanty but convincing evidence from collected chance occurrences that therapeutic irradiation of the maternal pelvis in pregnancy can determine malformations (Murphy, 1947).

(c) *The relationship of anomaly of the fœtus with specific disorders of pregnancy.*

Of disorders of pregnancy, hydramnios stands out in sharp relief as closely associated with a considerable variety of fœtal anomalies. Although present opinion appears to attribute hydramnios to a fœtal, rather than a maternal cause, it is remarkable how varied are the fœtal defects in a series of births where a high proportion of mothers have had hydramnios in the relevant pregnancies. Thus, although in most series hydramnios is recorded clinically as occurring in only about 1 per cent. of pregnancies, in a Belfast hospital the following approximate pro-

portions of mothers of malformed fœtuses had hydramnios :—anencephaly 60 per cent., Arnold-Chiari malformation 10 per cent., cleft palate (alone) 6 per cent., achondroplasia recognised at birth 50 per cent., occipital meningocœle (alone) 7 per cent. Further, the peculiarities may be noted of the association of hydramnios with twinning, a subject little investigated. Finally, there is the odd observation of Macafee (1950) confirmed by McMahon and McKeown (1952) of the high proportion of females affected, even in anencephaly, where the mother had hydramnios. Some association of diabetes in mothers and fœtal abnormalities has also been noted, but whether this is direct or a secondary association having hydramnios as the common factor is not at all clear. Finally, there is still difference of opinion about the effect on the fœtus of bleeding early in pregnancy.

(d) *The relationship of anomaly of the fœtus with parental age, maternal parity and familial aggregation of affected offspring.*

The effects of parental age and parity of the mother in varying the rates of congenital malformation in the offspring in man are not at all clear. In some studies this is because adequate control series in respect of normal births have not been available. In others any real effects on specific conditions may have been obscured by attempts to relate groups of clinically similarly afflicted offspring which were really of a heterogeneous morbid anatomy and ætiology.

Estimates so far made of familial incidence are usually confined to the incidence in the sibships of the index cases. In these sibships there seems frequently to be an aggregation of like defects so that the incidence in sibs is five or ten times that prevailing in all births. Perhaps in such estimates too little attention is paid to the contribution of a few exceptional women having several affected children. Thus, in the last year, I have seen one mother who had had five anencephalies and another who has had four children with pyloric stenosis. If such mothers had appeared by chance in a small series they would have contributed very markedly to the estimate of incidence.

The phenomenon of different defects occurring in the same sibship is also far from understood. Some reported instances are explicable as independent chance occurrences because fœtal malformations are relatively common, and certainly families individually reported showing such phenomena should be interpreted with caution. Probably more attention should be paid to the condition of the mother, when such aggregation of different defects occurs. In a few instances maternal genital malformation on fibroids is clearly related. In some of the neural tube syndromes occurring in the same family it seems likely that what are observed are really variations of the same defect.

B. The Types of Epidemiological Approach which have been made in the Past—Their Advantages and Disadvantages.

The difficulties of such investigations are considerable because, whatever be the starting point, fœtal and parental variables have to be related and the latter in turn to environmental variables. It is necessary therefore always to try to have fairly firm hypotheses to test in designing investigations using maternal or fœtal index

cases, and to have clearly in mind what parts of the enquiry are designed to consider the epidemiology of maternal states, and what fœtal states against a maternal background. Further, there is good reason to suspect that racial and/or geographic factors will determine considerable differences in different areas.

There have been many more investigations in recent years, and they seem to fall under a relatively small number of headings determined by kind of information collected and the methods used:—

There is the work done in analysing *series of congenital malformations occurring in hospitals,* using as controls the hospital births of unaffected infants. (Carter (1950), Ingalls, Pugh and McMahon (1954) and Coffey and Jessop (1955).) Essentially, in such investigations, with varying thoroughness and completeness, malformations in general and particular are related to the maternal variables—general health, disturbances of pregnancy, age, parity, and so on. Further, the reproductive histories of the mothers of malformed and non-malformed babies are usually compared. The weaknesses of such studies are readily recognised. There is selection which will vary from hospital to hospital of mothers of normal and of abnormal babies. Very often the diagnoses are in a small proportion by autopsy and the rest clinical. The series recorded are mostly retrospective (Coffey and Jessop being a notable exception) and therefore much depends on the completeness of information collected and the reliability of clinical notes which were not made specifically for the purpose in view. This applies particularly to the history of previous pregnancies and that of the exact condition of the child. Then very important information from the point of view of discerning the pattern of anomalies may be missing. Thus it is very uncommon to have consanguinity of parents or age of father recorded. Put another way, such series being invariably considered retrospectively tend to suffer from all the inherent associated disadvantages. The value of such studies is really exploratory, uncovering as they do suggestive phenomena which are subsequently far better investigated by *ad hoc* enquiries.

There have also been a few studies, most notably those from the Department of Social Medicine in Birmingham, where the *births of infants with anomalies in a defined area of population are related to all the births in the area over a period.* Such studies are big undertakings and are much more valuable in many ways than those which consider only hospital births, mainly because when properly planned they eliminate the biases. Inevitably there are also serious disadvantages, however essential such studies are for some purposes, and it would be unreasonable to expect them, however carefully planned, to answer all the questions we wish to pose on epidemiology. The difficulties lie mainly in obtaining retrospective information about the index pregnancy and even more in getting adequate confirmation of the mother's story about past pregnancies and their results. Even fewer autopsy records will be available than in hospital series.

When such studies are carried out, they must depend on many recorders of information. They cannot very readily deviate to examine the pattern of maternal or fœtal conditions in members of the family outside the sibship of the propositus. Nevertheless, the figures for frequency alone of specific defects, providing the best

checked information can be collected, are most valuable. Repeated under the same conditions in different areas they seem to be the only possible source (other than prospective studies) of defining the differences in frequency and relative frequency of specific defects which are known to exist for some anomalies in different areas and different racial groups.

Another method which has been used is to study *the reproductive performances of a group of mothers who had in common some anomaly of pregnancy or of reproductive organs*. This again is most likely to use hospital cases as a starting point, but that is not, of course, necessary. Under this heading will come the study of the offspring of diabetic mothers, of mothers with heart disease, mothers who had infections during pregnancy, mothers who had toxæmia, hydramnios and so on (Macafee, 1950). Similar problems are encountered of selection and of finding adequate controls as those mentioned previously. It is perhaps surprising how few such studies have been made. Possibly obstetricians still tend to be interested in anomalies of the mother mostly in so far as they effect her safe delivery. When the condition of the child is considered, too often the handling of the data is rather inadequate. Yet the method is surely as valid a starting point for observations as starting with the child, and is indeed an essential check on theories derived from the apparent association of a fœtal anomaly with a maternal condition.

Further, in considering these relationships, it seems essential to extend study to consider the familial incidence of the maternal anomaly if the true significance of the total familial pattern of the fœtal condition is to be seen in perspective. For example, hydramnios may be a familial condition and might be associated with different fœtal malformations in a given family.

Another series of observations which are often made are those on *bizarre families which are reported as curiosities in the medical literature*. Unfortunately such families are seldom adequately investigated or at least reported, so that unique information is lost. This is probably because the clinician who meets such an odd family has no particular interest or insight into the wider implications of his observations. Yet some of these families are of extreme interest and importance as in the example of the reporting by Bickers and Adams (1949) of a family with hereditary stenosis of the æqueduct of Sylvius which suggested for the first time that the pattern could be explained on the basis of an irregular dominant gene. Perhaps editors of journals could do more to improve the standard of such reporting than anyone.

C. A Résumé of the Gaps in Knowledge and in Past Epidemiological Work.

A number of points have been made in the course of this paper and it seems worth while stating them in summarized form. *First,* it has been suggested that most, if not all planned investigations of these phenomena in man would benefit immeasurably if carried out in an area where proper data were continually being collected about the reproductive pattern of all mothers so yielding the kind of background information made available in Birmingham (Record and McKeown,

1949). It does not seem too unreasonable to think that, with relatively little expense, health officers could collect and collate the necessary data from the home and hospital births in their areas. It may be remarked that health departments still tend to accumulate a wealth of social information, much of it apposite to past problems and in any case very difficult to interpret. Many appear uninterested, however, in the information on which an interpretation of the reproductive patterns of the areas depends.

Second, it seems clear that, in general, too few investigations have been planned and carried out to test specific hypotheses arising from the variety of sources already mentioned. There seem to have been very few enquiries indeed having as their starting point maternal characteristics and considering not only the mother's reproductive performance, but the familial incidence of the maternal characteristic and the reproductive performance of the *whole* family. Investigations using fœtal conditions as their starting point suffer from similar failures to investigate beyond the sibship of the propositus. It is remarkable that so little has been done to use autopsy findings as the source of index cases in collecting familial data. Thus "hydrocephalus" is still used as a diagnostic entity for which associations are sought, although at least a start has been made with the identification of several pathological types—most unlikely to have a common ætiology.

It seems likely that occipital meningocœle, Arnold-Chiari malformation, lumbo sacral meningomyelocœle and one type of anencephaly tending to iniencephaly and cranio-spinal-rachisis have a high incidence not only in sibs but in more distant members of the family. Poleman (1951), Dunn and Salter (1944) and Hiilsemaa (1955) have reported such instances and I have a number of families showing this pattern in my own series where autopsy records have been available for several malformed cousins. Little attention seems to have been paid to the observation of Murphy (1947) that in no instance did he encounter these central nervous system anomalies in the relatives of both parents; a finding so far confirmed in my own experience.

In atresia of the æqueduct group, the picture is quite different. In simple stenosis and forking of the æqueduct, the cases are isolated or occur with little variation in a high proportion of sibs or in other members of the family. A number of families I have seen conform to the suggestion of a single irregular dominant gene mechanism as suggested by Bickers and Adams (1949). All these observations need to be repeated and expanded. Studies of the offspring of twin brothers and sisters would be interesting.

Third, biologists keep assuming that recessive lethal genes in man contribute appreciably to fœtal wastage. So far there is little evidence for or against this hypothesis. Although a few lethal recessive genes are known, each is of very low frequency, with the exception of that determining fibrocystic disease of pancreas, and between them they cause a very small proportion of fœtal deaths. Until consanguinity data are available for a very large series of births it is difficult to see how these suggestions can begin to be investigated systematically.

Last, as has been pointed out, the relationship of abortion to fœtal anomalies in viable sibs in the same sibship has barely progressed beyond the stage of speculation.

D. Some Specific Suggestions for Epidemiological Investigations.

1. The rôle of hydramnios is clearly of the greatest importance and studies of the condition should be undertaken urgently, including the reproductive patterns of the index mother, of her sibs and of her husband's sibs.

It seems important to see whether, in a given family, hydramnios appears to be an inherited characteristic and in a given family, how dependent are any fœtal anomalies on hydramnios.

2. Other maternal anomalies such as fibroids and bicornate uterus could be studied by similar methods.

3. Using present autopsy separations of types of hydrocephalus and making some provisional separations of types of anencephaly it should be possible from any large maternity hospital having an adequate number of autopsies to plan investigations using fœtuses with deformed morbid anatomy as propositi.

In all the above, there is much need to relate such defined conditions to maternal states and gynæcological conditions and to carry out comprehensive familial investigations involving all cousins at least.

Such material is particularly suitable for the admittedly difficult task of trying to see if in some families at least the pattern could be reconciled with that determined by a translocation effect in animal work. It might be possible to show different varieties of anomaly, and although diminished fertility could not be demonstrated it would be worth while trying to see if in an otherwise regular menstrual history missed periods could be recalled (corresponding to implantation mole).

4. Serial examination of embryos recovered from spontaneous abortions could profitably be followed by using the abortion in the same way as a malformed fœtus for a comprehensive familial investigation.

5. There seems to be a worth while opportunity for statistical analysis of pairs or multiple defects syndromes, attempting to relate groups of defects occurring in a single child with each other and with what is known of embryological timings might yield valuable information as to the duration of action of numerous effects causing these malformations.

6. There is still room for prospective studies of the results of infections early in pregnancy and every opportunity should be taken to try to follow mothers through from the earliest possible times in pregnancy. To record, as is often done at present, only the month of pregnancy at which infection occurred when the week or even day must be known seems very unsatisfactory.

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REVIEW

A THERAPEUTIC INDEX. By C. M. Miller, M.D., M.R.C.P., and B. K. Ellenbogen, M.D., M.R.C.P. (Pp. xii + 148. 12s. 6d.) London: Baillière, Tindall & Cox, 1955.

It would appear that the aim of this work is to provide a pocket-book from which the practitioner or hospital resident will be able to obtain quickly a guide to the treatment of all the conditions he may meet. These conditions are dealt with alphabetically and range from "acid in the eye" to "trichinosis." This wide range of subject matter necessarily means that many important and common conditions receive inadequate attention.

In a short reference work of this type it may be considered curious that thrombophlebitis received only one quarter of the space devoted to tabes dorsalis.

The main criticism of this book is that the dangers of certain therapeutic measures advocated are not indicated. The intravenous administration of 1 mgm. of digoxin recommended for the treatment of left ventricular failure would certainly be hazardous when such failure followed myocardial infraction.

Despite its limitations, this index may be of some value to busy practitioners and housemen.

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